Remarks

This is in response to the final Office Action mailed April 22, 2002. Claims 151 and 152 have been added. New independent claim 151 corresponds with claims 82 and 95. New claim 152 corresponds with claims 115 and 127. Thus, the amendment is supported in the specification as filed, and does not raise new issues. No new matter has been added. Applicants respectfully request entry of the above amendment.

Rejections under 35 U.S.C. §103(a)

The claims are rejected as unpatentable over Bergman (US Pat. 5,501,955) in view of May et al. (US Pat. 5,622,871). The Janeway et al., Foster et al. (US Pat. 4,444,879), and Bergmann et al. (WO 95/06258) references are added to the rejections of specific dependent claims and the kit claims.

Applicants respectfully traverse the rejection raised by the Examiner under 35 U.S.C. 103 (a) against claims 82 - 96, 99 - 103, 107, and 146 - 149 as being unpatentable over Bergman and May et al. Applicants submit that a possible combination of a conventional test tube immunological reaction as described in Bergman, with the capillary device as described in May et al, cannot be viewed as routine and well-known in the art as suggested by the Examiner. Although on an initial consideration of prior art documents Bergman and May et al, the combination thereof might seem to be a straightforward approach, Applicants believe this not to be the case. Applicants believe that when the specific disclosures and teachings of prior art documents Bergman and May et al, are taken into account, together with the state of the art techniques and expertise in the field of immunology, the approach suggested by the Examiner would not have represented a routine and well-known procedure at the priority date of US Patent Application 09/582524. The reduction to practice of a method as defined in the claims 82 - 96, 99 - 103, 107, and 146 - 149 does not represent a mere combination of the features described and taught in prior art documents Bergman and May et al. Applicants respectfully request that the Examiner further considers the detailed teachings respectively provided by Bergman and May et al, and in particular the specific reagents and conditions described therein, and respectfully request that the Examiner advises Applicants as to why the Examiner considers as routine the necessary modifications of

these prior art reagents and conditions that would have been required in order to arrive at a method as defined in claims 82 - 96, 99 - 103, 107, and 146 - 149.

Applicants further submit that the above can be substantiated by reference to the development of the prior art in the field of test tube and capillary assays.

Bergman relates to the use of conventional test tube immunological reaction conditions for screening for autoantibodies to TPO and that incubation of the reagents employed would have been required. Known modifications of such conventional test tube conditions as described in Bergman have to date included, for example, immunofluorescence techniques; particle agglutination inhibition assays using a variety of particles; ELISA using anti-human IgG peroxidase or similar conjugate; sandwich assays using TPO coated tubes and protein A or anti-human IgG labeled with 125I or non-isotopic material; immunoprecipitation assays in which complexes of TPO autoantibodies and 125I-labelled TPO are precipitated by addition of solid phase protein A (magnetic or non-magnetic) or anti-human IgG; inhibition assays employing TPO monoclonal antibody coated tubes and TPO labeled with 125I or with non-isotopic material; and bridging assays in which the divalent nature of TPO autoantibodies is used to link liquid phase labeled (isotopically labeled or non-isotopically labeled) TPO to TPO immobilized on a solid support. The Examiner will appreciate that considerable research has, therefore, been carried out into optimization or modification of known techniques for use in immunoassays of the type described in Bergman, but none of this research has been directed at, or suggested, modification to a capillary device of the type described in May et al and as suggested by the Examiner. The above comments can be reinforced by further reference to Bergman where, for example, possible variations of the invention are described (the different embodiments of the invention described with reference to Figures 1, 2 and 3) and various reaction conditions and reagents are discussed for use in the test tube assays disclosed therein, there being nothing in the disclosure or teaching of Bergman that might have pointed to a capillary test device of the type taught by May et al. To the contrary, as explained above lines 42 to 52 of column 6 of Bergman specify that the solid substrate and conditions employed in the subject immunological reactions should not differ fundamentally from other conventional immunological assay methods. Furthermore, the fact that modification of the test tube assays described in Bergman as

suggested by the Examiner was in no way contemplated by Bergman can be seen with reference to, for example, the labels described in Bergman. For example, claim 5 describes possible labels as being selected from the group consisting of "a radioactive isotope, an enzyme, a fluorescent label, a chemiluminescent label, and a substrate for an enzymatic detection reaction". These labels are suitable for use in test tube type assays as described in Bergman but do not represent labels most practically employed in a strip device of the type taught in May et al. As such, there is no contemplation or suggestion in Bergman of the modification now put forward by the Examiner, otherwise Bergman would have suggested the use of labels of the type most suitable for use in a strip device of the type taught in May et al, such as coloured particles, for example colloidal gold.

May et al relate to a capillary immunoassay testing device, where antibodies are employed as specific binding reagents for an analyte antigen. May et al provide no enabling teaching as to how such a capillary immunoassay test device might be modified to screen for autoantibodies rather than antigens. Indeed, although antibodies are discussed extensively in the specification of May et al, any enabling disclosure in this respect is solely in the context of reagent not analyte. Furthermore, capillary test devices of the type described in May et al have been known for a number of years. Modifications and optimization of such capillary devices have been carried out during that time, for example in terms of substrate materials and test reagents. To the Applicant's knowledge, however, there was at the priority date of US Patent Application 09/582524 no published literature, and furthermore there still has been no published literature, that suggested or might have suggested an assay method as defined in claims 82-96, 99-103, 107 and 146-149. Applicants submit it is only with the knowledge of the present invention that such modifications might be routinely considered and that the Examiner is able to raise an objection to lack of inventive step of a method as defined in claims 82 - 96, 99 - 103, 107, and 146 - 149.

Applicants respectfully traverse the Examiner's objection under 35 U.S.C. 103 (a) against claims 115-145 and 150 as being unpatentable over Bergman, May et al and Foster et al. Applicants refer the Examiner to the above mentioned comments with respect to Bergman and May et al in relation to method claims 82-96, 99-103, 107 and 146-149 and submit these similarly apply to claims 115-145 and 150. Applicants further

submit that the teaching provided by Foster et al would in no way have advanced the teaching of the prior art so as to provide motivation or guidance for providing a kit as defined in claims 115-145 and 150. Applicants respectfully request withdrawal of the objection.

Applicants wish to also direct the Examiner's attention to rejections of the following specific claims.

New claims 151 and 152 (and pending dependent claims 95 and 127) require a substrate having an application zone containing antigen that is upstream of a region of immobilized antibody, with the antigen being capable of binding both the immobilized antibody and the autoantibody to be detected. None of the cited references teach or suggest a method involving the claimed substrate. Bergman teaches an assay performed in a test tube, and May et al. teach an assay involving a porous carrier. Bergman teaches embodiments where test tube assays are employed to detect autoantibodies to TPO, where a sample to be investigated is contacted with two monoclonal antibodies and an antigen, namely TPO. The monoclonal antibodies comprise an immobilized antibody and a freely labeled antibody against the antigen. Applicants submit that if the Examiner were to consider in detail the interaction of the above referred to monoclonal antibodies, antigen and autoantibodies as described in Bergman, the Examiner would appreciate that if the antigen were to be immobilized to a substrate, such as the coated test tubes described in Bergman, detection of autoantibodies would not be possible whilst employing the remaining techniques taught by Bergman. It would, therefore be completely contrary to the teaching of Bergman to provide an antigen on an application zone of a substrate as is now defined in new claims 151 and 152. Furthermore, May et al. teach an embodiment in which the porous carrier has immobilized antibodies and a labeled free reagent, but the labeled free reagent and immobilized antibody both bind the analyte. The instant invention is distinguished because the antigen initially provided on the substrate can either bind autoantibodies to be detected in the sample or the immobilized antibody. There is no motivation or guidance in the prior art for performing a method as instantly claimed. Applicants respectfully request withdrawal of the rejection of pending claims 95 and 127, and submit that new claims 151 and 152 are distinguished over the prior art.

Claims 105 and 106 are directed to an assay for two different autoantibodies, and claim 106 requires the use of a single antigen with two distinct binding sites, one to each of the two autoantibodies to be measured. The single antigen serves as a specific binding reagent for detecting two different autoantibodies. None of the cited references teach or suggest such an assay. Bergman teaches a test tube assay for detecting a single autoantibody. May et al. teach a capillary assay that can be used for detecting multiple analytes, but specifically teach using "different specific binding agents" to provide the multi-analyte test (see column 6, lines 10-12). Thus, there is no motivation or guidance for one of ordinary skill in the art to have modified the assay of Bergman to achieve the instantly claimed method. Applicants respectfully request withdrawal of the rejection.

With respect to claim 111, Janeway et al. is relied upon for teaching multivalent antigens and antibody binding, and monoclonal antibody production. The Examiner asserts that, while Bergman and May et al. admittedly do not teach the detection of two autoantibodies in the same assay, it would have been obvious to modify the methods of Bergman and May et al. to include multivalent antigen and monoclonal antibodies specific for the pertinent epitopes, as taught by Janeway et al., to achieve a selective and sensitive assay for dual analyte detection. Applicants respectfully traverse the rejection.

As stated in previous arguments, Bergman and May et al are directed to different assay formats (test tube and capillary test strip, respectively) for the detection of single analytes. The only motivation and guidance for one of ordinary skill in the art to modify the assay of Bergman to achieve the instantly claimed assay is found in Applicants' disclosure. The Examiner has not provided a teaching or reasoning (other than that found in the instant specification) in support of the assertion that one would have been motivated to modify the assay of Bergman according to May et al. and Janeway et al. to achieve an assay for detecting at least first and second autoantibodies. Additionally, Applicants submit that even if one were to attempt such modification of Bergman, there is no reasonable expectation of success in achieving a functional and useful assay. Upon reading Bergman, May et al. and Janeway et al., one of ordinary skill in the art would know how to perform a test tube assay for autoantibodies, perform a test strip assay for analytes such as hCG, and make monoclonal antibodies against multivalent antigens.

However, one would not have a reasonable expectation of success in performing the assay instantly claimed. Applicants respectfully request withdrawal of the rejection.

Claim 142 was rejected as obvious over Bergman in view of May et al. and further in view of Foster et al. Foster et al. was relied upon for teaching an immunoassay kit containing various reagents for performing an immunoassay. The Examiner asserted that it would have been obvious to incorporate the reagents of Bergman and May et al. into a kit, as taught by Foster et al., because kits are well known in the art and widely recognized for their advantages of economy and convenience. Applicants respectfully traverse the rejection.

None of Bergman, May et al, or Foster et al. teaches or suggests a kit containing the specific reagents required in claim 142. Additionally, none of the cited references provide the motivation or guidance for performing an assay utilizing the claimed reagents, as stated above. Therefore, one would not have been motivated to combine the specific reagents required by the claims into a kit. Applicants respectfully request withdrawal of the rejection.

Claim 150 was rejected as unpatentable over Bergman in view of May et al. and further in view of Foster et al. Applicants respectfully traverse the rejection. None of the cited references teach or suggest combining reagents for performing an immunoassay for detecting autoantibodies with at least one therapeutically active substance effective in the treatment of an autoimmune disease, as is required by the present claim. Additionally, the Examiner has not provided any reasoning as to why one would have been motivated to make such a modification to Bergman, given the teachings of May et al. and Foster et al. Applicants respectfully request withdrawal of the rejection.

Conclusion

In view of the amendments and comments presented herein, favorable reconsideration is respectfully requested.

Respectfully submitted,

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